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I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.**1247/Del/2003** dated **08th October 2003**.*

Witness my hand this 17th day of February 2005.

(S.K. PANGASA)
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COMPLETE SPECIFICATION

(See Section 10)

STABLE PAROXETINE COMPOSITIONS AND PROCESS FOR THEIR PREPARATION

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A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to stable pharmaceutical compositions of paroxetine and process for preparation thereof.

Paroxetine, (-) – trans-3- [(1, 3 – benzodioxol – 5 – yl oxy) methyl] – 4 – (4 – fluorophenyl) piperidine; (3S, 4R) – 3 – [5 – (1, 3 – dioxaindanyl) oxy methyl] – 4 – (p – fluorophenyl) piperidine, is a 5 – hydroxy tryptamine (5 – HT, serotonin) re-uptake inhibitor, and is disclosed in US Patent No. 4,007,196. It is indicated for the treatment of psychiatric problems including depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorders and post-traumatic stress disorder and other symptoms associated with excessive serotonin release. It is marketed as both immediate release and controlled release tablets by Glaxo Smith Kline under the trade names of Paxil® and Paxil®CR, respectively.

Paroxetine dosage forms are often associated with certain physical instabilities, depending on excipients used and the method of their preparation; like development of a pink hue, softening of the dosage form or decrease in hardness upon storage. Skillful selection of pharmaceutically inert excipients and controlled manufacturing processes are thus necessary to obtain paroxetine dosage forms having the desired properties.

Few strategies and methods have been proposed and used to overcome these problems. For example US Patent No. 6, 113, 944, assigned to Smith Kline Beecham attributes the development of undesirable pink hue on paroxetine tablets to water used during processing and discloses a process in which water is avoided to overcome this problem.

PCT Application No. WO 03/057150, filed by Teva Pharmaceutical Industries Ltd., discloses that paroxetine tablets containing hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC), the two most widely accepted excipients, lose their mechanical stability on storage leading to breaking of the dosage forms. Further it suggests that this problem can be overcome by preparing paroxetine tablet free of HPMC and a filler that is non hygroscopic and free of hydrochloric acid (HCl). In particular it excludes the use of one of widely used conventional filler, MCC and binder HPMC. HPMC is also widely used as modified release polymer.

There thus exists a need for paroxetine dosage forms using conventionally used excipients.

We have now surprisingly developed an easy and simple process for preparing stable paroxetine compositions using conventionally used excipients and prepared by wet granulation, which is one of the widely accepted and most frequently used technique.

Hence, in one aspect there is provided a stable pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose as a filler, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another aspect there is provided a stable modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, at least one modified release polymer, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another aspect there is provided a stable modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, hydroxypropyl methylcellulose, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another aspect there is provided a process for preparing a stable pharmaceutical composition of paroxetine which comprises the steps of wet granulating paroxetine, microcrystalline cellulose and optionally other pharmaceutically inert excipients; drying and sizing the granules; lubricating the granules; and processing into suitable dosage form.

In another aspect there is provided a process for preparing a stable, modified release pharmaceutical composition of paroxetine which comprises the steps of wet granulating paroxetine, microcrystalline cellulose, at least one modified release polymer, and optionally other pharmaceutically inert excipients; drying and sizing the granules; lubricating the granules; and processing into suitable dosage forms.

In another aspect there is provided a process for preparing a stable, modified release pharmaceutical composition of paroxetine which comprises the steps of wet granulating paroxetine, microcrystalline cellulose, hydroxypropyl methyl cellulose, and optionally other pharmaceutically inert excipients; drying and sizing the granules; lubricating the granules; and processing into suitable dosage forms.

In another aspect there is provided a method of treating depression by administering to a subject in need thereof, a stable pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another aspect there is provided a method of treating depression by administering to a subject in need thereof, a stable, modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, at least one modified release polymer, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another aspect there is provided a method of treating depression by administering to a subject in need thereof, a stable, modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, hydroxypropyl methyl cellulose, and optionally other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

The pharmaceutical compositions of paroxetine as described in the present invention is prepared by the widely acclaimed wet granulation technique, using MCC, a conventionally used filler, and HPMC as modified release polymer, without encountering the physical instabilities of development of pink hue and decrease in hardness upon storage, as shown in Table 1. The preparation of granulation for tabletting by wet granulation process is the oldest and still the most widely used. Further, MCC, being a porous material promotes easy wetting and rapid drying of wet granulation and exhibits good flow characteristics with low lubricant demand.

The term 'stable' as used herein refers to mechanically stable pharmaceutical composition of paroxetine, wherein the composition does not loose its hardness or

develop pink coloration even after storage at a temperature of 40°C and 75% relative humidity for at least 5 days.

The term 'paroxetine' as used herein includes paroxetine and its pharmaceutically acceptable salts such as hydrochloride, orthophosphate, benzoate, maleate, tartarate, succinate, citrate, acetate and mesylate; hydrates and solvates thereof. In particular paroxetine hydrochloride hemihydrate may be used.

The term 'pharmaceutical composition' as used herein refers to solid dosage form for oral administration like tablet, capsule, pill, spheroid, granule and the like. Among these tablets may be particularly used.

The term "modified release dosage form" as used herein includes any modified release formulation intended for slow release such as controlled release, prolonged release, delayed release, timed release etc.; capable of modifying the release of the drug up to a period of about 12 hours. In particular delayed release dosage form may be used.

The term 'wet granulation' as used herein refers to granulation using water miscible solvent(s), with or without water. Examples of such water miscible solvents include lower alcohols such as ethanol and isopropyl alcohol (IPA); lower ketones such as acetone. In particular mixture of water and IPA may be used.

MCC is purified partially de-polymerized alpha-cellulose. The de-polymerization is catalyzed by hydrochloric acid. It is white, odorless, tasteless free flowing powder, which is insoluble in water, dilute acids and in most organic solvents and is practically insoluble in sodium hydroxide solution. The concentration of MCC may range from about 15% to 45% by weight. In particular MCC at a concentration of about 30% may be used. It is commercially available under the trade name of Avicel® (manufactured by FMC Corporation) in various grades such as PH 103, PH 105, PH 101, PH 113 and PH 301. Amongst these Avicel® PH 101 may be particularly used.

Modified release polymers include cellulose derivatives, alginic acid derivatives methacrylic acid derivatives, polysaccharides, alkylene oxides, and the like and combinations thereof. Specific examples of cellulose derivatives include HPMC, hydroxypropyl cellulose (HPC), methylcellulose, carboxymethyl cellulose, hydroxyethyl

cellulose, and the like and combinations thereof. Alginic acid derivative as used herein include both alginic acid and its physiologically acceptable salts such as those of sodium, potassium, calcium and the like and combinations thereof. Examples of methacrylic acid derivatives include the various grades available under the trade name of Eudragit®. Examples of polysaccharides include chitosan, gellan, xanthan and the like and combinations thereof. Examples of alkylene oxide include polyethylene oxide.

HPMC is a cellulose ether, derived from alkali treated cellulose that is reacted with methyl chloride and propylene oxide. It has several names including 2-hydroxy propyl ether of methyl cellulose, propylene glycol ether of methyl cellulose, 2-hydroxy propyl methyl ether, hypromellose etc. It is widely used as a modified release polymer, binder and in coating compositions and is commercially available as Methocel® (manufactured by Dow Chemicals) in various viscosity grades. The concentration of HPMC may range from about 10% to about 30% by weight. In particular HPMC at a concentration of about 15% may be used. Examples of HPMC of low viscosity grade include Methocel E-5, Methocel E-15 LV, Methocel E-50 LV, Methocel K-100 LV and Methocel F-50 LV, whose 2% w/v aqueous solutions have viscosities of 5 cPs, 15 cPs, 100 cPs and 50 cPs, respectively. Examples of HPMC of medium viscosity grade include Methocel E4M and Methocel K4MCR, whose 2% w/v aqueous solutions have a viscosity of 4000 cPs. Examples of high viscosity grade include Methocel K15M and Methocel K 100 M whose 2% w/v aqueous solutions have viscosities of 15,000 and 10,000 cPs, respectively. Among these Methocel K4MCR and Methocel E-15 LV may be particularly used.

Examples of pharmaceutically acceptable inert excipients include wetting agents, fillers, binders, disintegrants, coloring agents, flavoring agents, stabilizers, lubricants/glidants and plasticizers.

Examples of wetting agents include both ionic and non-ionic wetting agents. These include polyethylene glycols; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; polyglycerin fatty acid ester such as decaglyceryl monolaurate and decaglyceryl monomyristate, polyoxyethylene sorbitan fatty acid ester such as polyoxyethylene sorbitan monooleate, polyethylene glycol fatty acid ester such as polyoxyethylene monosterate, polyoxyethylene alkyl ether such as poluoxyethylene lauryl ether; polyoxyethylene castor oil and hardened castor oil, such as polyoxyethylene hardened castor oil; sucrose ester of fatty acid such as sucrose state

ester and sucrose palmitate ester and alkyl sulfate salt such as sodium lauryl sulfate and magnesium lauryl sulfate; sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Examples of fillers include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and the like and combinations thereof.

Examples of binders include polyvinyl pyrrolidone, methylcellulose, hydroxypropyl cellulose, HPMC, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol and the like and combinations thereof.

Examples of disintegrants include croscarmellose sodium, crospovidone, carboxymethyl starch sodium, sodium starch glycollate and the like and combinations thereof.

Examples of lubricants and glidants include colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like and combinations thereof.

Examples of plasticizers include polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate, and the like and combinations thereof.

Examples of stabilizers include antioxidants, buffers, acids and the like and combinations thereof.

Examples of coloring agents include any FDA approved colors for oral use.

In one of the embodiments there is provided a stable pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, another filler, binder,

disintegrant and lubricant / glidant, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another embodiment there is provided a stable, modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, at least one modified release polymer, another filler, binder, disintegrant and lubricant / glidant, wherein the pharmaceutical composition is prepared by wet granulation technique.

In another embodiment there is provided a stable, modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, hydroxypropyl methylcellulose, another filler, binder, disintegrant and lubricant / glidant, wherein the pharmaceutical composition is prepared by wet granulation technique.

In one of the embodiments, there is provided a process for preparing a stable pharmaceutical composition of paroxetine, which process comprises the steps of (a) blending paroxetine with microcrystalline cellulose, another filler, binder and disintegrant (b) wet granulating the blend and drying to form granules (c) lubricating the granules and compressing into tablets.

In one of the embodiments, there is provided a process for preparing a stable modified release pharmaceutical composition of paroxetine, which process comprises the steps of (a) blending paroxetine with microcrystalline cellulose, at least one modified release polymer, another filler, binder and disintegrant (b) wet granulating the blend and drying to form granules (c) lubricating the granules and compressing into tablets.

In one of the embodiments, there is provided a process for preparing a stable modified release pharmaceutical composition of paroxetine, which process comprises the steps of (a) blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, another filler, binder and disintegrant (b) wet granulating the blend and drying to form granules (c) lubricating the granules and compressing into tablets.

The tablets prepared by any of the above embodiments may further be coated with conventional film-forming polymers and / or modified release polymer, in particular enteric polymer to provide delayed release of the drug.

Examples of film-forming polymers include ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethyl cellulose, hydroxyethyl cellulose; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit® RL and RS; and the like; and combinations thereof. Alternatively, coating may be performed using commercially available ready to coat preparations such as various grades of Opadry®.

Examples of enteric polymer include cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methycellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L 30, Eudragit® D55, Eudragit® L 100, Eudragit® S 100; and the like and combinations thereof. Enteric coating may be continued up to a weight gain of about 1% to about 50% of the total weight. In particular, enteric coating may be continued up to a weight gain of about 1% to about 10% of the total weight and more particularly, up to a weight gain of about 5% to 10% of the total weight.

In another embodiment, there is provided a process for preparing a stable modified release pharmaceutical composition of paroxetine, which process comprises the steps of (a) blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, lactose monohydrate and polyvinyl pyrrolidone (b) wet granulating the blend and drying to form granules (c) lubricating the granules and compressing into tablets (d) enteric coating the tablet up to a weight gain of 8-10% and (e) further coating with Opadry® up to a weight gain of 2-3%.

The invention is further illustrated by the following examples, which is for illustrative purpose and should not be construed as limiting the scope of the invention in any way.

Examples 1-2

Ingredients	Amount (mg / tab)	
	Ex-1	Ex-2
Paroxetine hydrochloride hemihydrate	44.25	44.25
Hydroxypropyl methylcellulose (medium viscosity)	20.0	20.0
Hydroxypropyl methylcellulose (low viscosity)	5.0	5.0
Microcrystalline cellulose	50.0	50.0
Lactose monohydrate	40.0	55.0
Polyvinyl pyrrolidone	10.0	10.0
Water	qs	Qs
Iso propyl alcohol	qs	Qs
Magnesium stearate	3.0	3.0
Talc	2.75	2.75

Procedure

For the preparation of tablets of paroxetine hydrochloride hemihydrate as per examples 1-2, the drug was blended with other solid ingredients (except magnesium stearate and talc) and granulated with a mixture of water and iso propyl alcohol (4:96 v/v) and dried.

The dried granules were blended with magnesium stearate and talc and compressed into tablets. Compressed tablets were further enteric coated using Eudragit® L-100-55 dispersion up to a weight gain of 8-10 % w/w and the enteric coated tablets were further coated with Opadry® up to a weight gain of 2-3% w/w.

The hardness and friability of the prepared tablets were tested immediately and after 15 days of storage at 40°C and 75% relative humidity using a Monsatto hardness tester and Roche's friabilator, respectively. The data is shown in Table 1.

Table 1: Hardness of Paroxetine hydrochloride hemihydrate tablets

Period	Hardness (Kp)		Friability (%)	
	Ex-1	Ex-2	Ex-1	Ex-2
Initial	9-11	9-11	0.45	0.02
After 15 days	9-11	9-11	0.38	0.06

The tablets of Examples 1 and 2 were tested for *in vitro* release of paroxetine hydrochloride hemihydrate in USP type II dissolution apparatus with #10 sinker at 100 rpm and temperature of 37±0.5°C, in 500 ml of 0.1N hydrochloric acid for 2 hours and then transferred to 900 ml of pH 6.8 buffer for the remaining period. 10 ml samples were withdrawn at pre-determined intervals and replaced with an equal volume of the appropriate pre-warmed dissolution medium. The withdrawn samples were analyzed for paroxetine hydrochloride hemihydrate content after appropriate dilution. The results of the study are shown in Table 2.

Table 2: *In vitro* release profile of paroxetine hydrochloride hemihydrate from the prepared tablets

Time (h)	Cumulative percentage (%) of paroxetine hydrochloride hemihydrate released	
	Ex-1	Ex-2
2	0	1
3	5	5
4	12	11
5	22	19
6	30	30
8	51	54
10	68	77
12	81	93
14	90	101

WE CLAIM:

1. A stable pharmaceutical composition of paroxetine, comprising paroxetine, microcrystalline cellulose and other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by a wet granulation technique.
2. The stable pharmaceutical composition according to claim 1, wherein paroxetine is selected from free paroxetine and pharmaceutically acceptable salts, hydrates and solvates thereof.
3. The stable pharmaceutical composition according to claim 2, wherein the pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, orthophosphate, benzoate, maleate, tartarate, succinate, citrate, acetate and mesylate.
4. The stable pharmaceutical composition according to claim 3, wherein the pharmaceutically acceptable salt is paroxetine hydrochloride.
5. The stable pharmaceutical composition according to claim 4, wherein the paroxetine hydrochloride is paroxetine hydrochloride hemihydrate.
6. The stable pharmaceutical composition according to claim 1, wherein the concentration of microcrystalline cellulose may vary from about 15 % to about 45% by weight.
7. The stable pharmaceutical composition according to claim 6, wherein the concentration of microcrystalline cellulose is about 30% by weight.
8. The stable pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable inert excipient is selected from the group consisting of fillers, binders, disintegrants, wetting agents, stabilizers, plasticizers, lubricants / glidants, flavouring agents and colouring agents.

9. The stable pharmaceutical composition according to claim 1, wherein wet granulation is carried out using water miscible solvent, with or without water.

10. The stable pharmaceutical composition according to claim 9, wherein water miscible solvent is selected from the group consisting of lower alcohols such as ethanol, isopropyl alcohol and lower ketones such as acetone.

11. The stable pharmaceutical composition according to claims 9 and 10, wherein the wet granulation is carried out using a mixture of water and isopropyl alcohol.

12. The stable pharmaceutical composition according to claim 1, wherein pharmaceutical composition is a solid dosage form selected from tablet, capsule, caplet, spheroid, and granule.

13. The stable pharmaceutical composition according to claim 12, wherein the solid dosage form is a tablet.

14. The stable pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is coated with a non-functional film-forming polymer.

15. A process for the preparation of a stable pharmaceutical composition of paroxetine, which comprises the steps of (a) blending paroxetine, microcrystalline cellulose and other pharmaceutically acceptable inert excipients; (b) wet granulating the blend; (c) drying and sizing the granules; (d) lubricating the granules and processing into suitable dosage form.

16. A stable, modified release pharmaceutical composition of paroxetine, comprising paroxetine, microcrystalline cellulose, at least one modified release polymer, and other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by a wet granulation technique.

17. The stable modified release pharmaceutical composition according to claim 16, wherein the modified release polymer is selected from the group comprising of cellulose derivatives such as hydroxypropyl methylcellulose, hydroxypropyl

cellulose, methylcellulose, carboxymethyl cellulose, hydroxyethtyl cellulose; alginic acid derivatives such as sodium, potassium, and calcium salts of alginic acid; methacrylic acid derivatives polysaccharides such as chitosan, gellan; alkylene oxides such as polyethylene oxide and combinations thereof.

18. The stable, modified release pharmaceutical composition according to claim 17, wherein the modified release polymer is hydroxypropyl methyl cellulose.

19. A stable, modified release pharmaceutical composition of paroxetine, comprising paroxetine, microcrystalline cellulose, hydroxyypropyl methylcellulose, and other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by a wet granulation technique.

20. The stable modified release pharmaceutical composition according to claims 16 or 19, wherein paroxetine is selected from free paroxetine and pharmaceutically acceptable salts, hydrates and solvates thereof.

21. The stable modified release pharmaceutical composition according to claim 20, wherein the pharmaceutically acceptable salt is selected from the group consisting of hydrochloride, orthophosphate, benzoate, maleate, tartarate, succinate, citrate, acetate and mesylate.

22. The stable modified release pharmaceutical composition according to claim 21, wherein the pharmaceutically acceptable salt is paroxetine hydrochloride.

23. The stable modified release pharmaceutical composition according to claim 22, wherein the paroxetine hydrochloride is paroxetine hydrochloride hemihydrate.

24. The stable pharmaceutical composition according to claims 16 or 19, wherein the concentration of microcrystalline cellulose may vary from about 15% to about 45% by weight.

25. The stable pharmaceutical composition according to claim 24, wherein the concentration of microcrystalline cellulose is about 30% by weight.

26. The stable modified release pharmaceutical composition according to claims 18 or 19, wherein hydroxypropyl methylcellulose is selected from the low, medium and high viscosity grades or combinations thereof.

27. The stable, modified release pharmaceutical composition according to claims 18 or 19, wherein the concentration of hydroxypropyl methylcellulose may vary from about 10% to about 30% by weight.

28. The stable, modified release pharmaceutical composition according to claim 27, wherein the concentration of hydroxypropyl methylcellulose is about 15% by weight.

29. The stable modified release pharmaceutical composition according to claims 16 or 19, wherein the pharmaceutically acceptable inert excipient is selected from the group consisting of fillers, binders, disintegrants, wetting agents, stabilizers, plasticizers, lubricants / glidants, flavouring agents and colouring agents.

30. The stable modified release pharmaceutical composition according to claims 16 or 19, wherein wet granulation is carried out using water miscible solvent, with or without water.

31. The stable modified release pharmaceutical composition according to claim 30, wherein water miscible solvent is selected from the group consisting of lower alcohols such as ethanol, isopropyl alcohol and lower ketones such as acetone.

32. The stable modified release pharmaceutical composition according to claims 30 and 31, wherein the wet granulation is carried out using a mixture of water and isopropyl alcohol.

33. The stable modified release pharmaceutical composition according to claims 16 or 19, wherein pharmaceutical composition is a solid dosage form selected from the group consisting of tablet, capsule, caplet, spheroid, and granule.

34. The stable modified release pharmaceutical composition according to claim 33, wherein the solid dosage form is a tablet.

35. The stable modified release pharmaceutical composition according to claims 16 or 19, wherein the pharmaceutical composition is coated with an enteric polymer.

36. The stable modified release pharmaceutical composition according to claim 35, wherein the enteric polymer is selected from the group consisting of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers such as Eudragit® L 100-55, Eudragit® L 30, Eudragit® D55, Eudragit® L 100, Eudragit® S 100; and combinations thereof.

37. The stable modified release pharmaceutical composition according to claim 36, wherein the enteric polymer is methacrylic acid copolymer.

38. The stable modified release pharmaceutical composition according to claim 35, wherein the enteric coat gives a weight gain of about 1% to about 50% of the total weight.

39. The stable modified release pharmaceutical composition according to claim 38, wherein the weight gain is about 1% to about 10% of the total weight.

40. The stable modified release pharmaceutical composition according to claim 39, wherein the weight gain is about 5% to about 10% of the total weight.

41. The stable modified release pharmaceutical composition according to claim 35, wherein the pharmaceutical composition is further coated with a non functional film-forming polymer.

42. A process for the preparation of a stable modified release pharmaceutical composition of paroxetine, which comprises the steps of (a) blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, fillers, binders and disintegrants; (b) wet granulating the blend; (c) drying and sizing the granules; (d)

lubricating the granules and compressing into tablets (e) enteric coating the tablet up to a weight gain of 8-10% and (f) finally film coating up to a weight gain of 2-3%.

43. A method of treating depression by administering to a subject in need thereof a stable pharmaceutical composition of paroxetine comprising paroxetine microcrystalline cellulose, and other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

44. A method of treating depression by administering to a subject in need thereof a stable modified release pharmaceutical composition of paroxetine comprising paroxetine, microcrystalline cellulose, hydroxypropyl methylcellulose, and other pharmaceutically acceptable inert excipients, wherein the pharmaceutical composition is prepared by wet granulation technique.

Dated this 7TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

STABLE PAROXETINE COMPOSITIONS AND PROCESS FOR THEIR PREPARATION

Stable pharmaceutical composition of paroxetine with microcrystalline cellulose as filler is disclosed. Further, a process for preparing the stable pharmaceutical composition of paroxetine using a wet granulation technique is also disclosed.